intestinal microbiota may contribute to progression of chronic liver damage, especially liver fibrogenesis [8], which in turn may aggravate not only installed cirrhotic lesions through increased inflammation and fibrosis, but also accelerate or provoke progression of NASH and alcoholic steatohepatitis to cirrhosis. Thus, the role, in humans, of BT in the progression of chronic hepatic damage, both in installed cirrhosis and precirrhotic lesions, may appear of paramount importance, in conjunction with persistent alcohol consumption in cases of alcoholic chronic liver disease and cirrhosis. There is increasing suggestive evidence that bacterial translocation and intestinal flora dysfunction are associated with the development of liver fibrosis [9], and that bacteria and microbial products, including endotoxins – like lipopolysaccharides (LPS) macromolecules, the major molecular component of the outer membrane of Gram-negative bacteria –, bacterial DNA or microbial metabolites – like ethanol produced by the intestinal microbiome or choline – may contribute to the pathogenesis of NAFLD and NASH, and presumably to progression to overt cirrhosis due to increased fibrogenesis [6]. Finally, this clearly suggests the possible associated role of chronic, repetitive BT, not only in mesenteric lymph nodes but also in portal blood and the liver itself [10], as elicited by a chronically leaky intestine (which may precede and/or be the consequence of cirrhosis and be aggravated – in alcohol-induced chronic liver disease – by persistent chronic alcohol consumption), in cirrhosis pathogenesis itself.

Conflict of interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Reply to: "Bacterial translocation in liver cirrhosis: Site and role in fibrogenesis"

To the Editor:
We greatly appreciate the comments raised by Dr Matuchansky regarding our recent review on pathological bacterial translocation (BT) in liver cirrhosis [1]. As for the site of BT in cirrhosis we acknowledge the investigation in compensated cirrhotic patients utilizing a multisugar test [2]. The study described by Dr Matuchansky reports in cirrhotic individuals an increased sucralose/erythritol ratio in 5–24 h urine (supposed to indicate colonic permeability) whereas the lactulose/rhamnose ratio in 0–5 h urine (supposed to represent small intestinal permeability) was not altered. This study has not been cited by us due to (i) the fact, that any information gained by using sugar tests most likely does not reflect permeability to macromolecules such as bacteria and/or bacterial cell wall components, (ii) criticisms related to methodological issues in performance of those sugar tests [3–5], and finally (iii) the limitation in references to be used. Sugars utilized in those permeability tests are very small molecules (182–400 Da) whose passage across the mucosal barrier is not necessarily related to structural damage in the tight junction barrier that permits increased penetration of large molecules (e.g., lipopolysaccharide can reach up to 100,000 Da). Moreover, although not convincingly proven at least for living bacteria, likewise larger in size than mono-/disaccharides, BT occurs most likely via transcytosis (Fig. 1). Transcytosis of vital bacteria however is complex, includes active sampling by dendritic cells and transport across M cells as well as epithelial cells all of which is regulated different from transport of sugars in terms of initiation, kinetics and host response. Therefore, also others have proposed that measuring permeability to small sugar molecules does not correlate with gut dysbiosis, endotoxin release, microbial translocation and/or activation of the mucosal immune system [6,7]. Mucosal defense mechanisms (e.g., number and secretion of

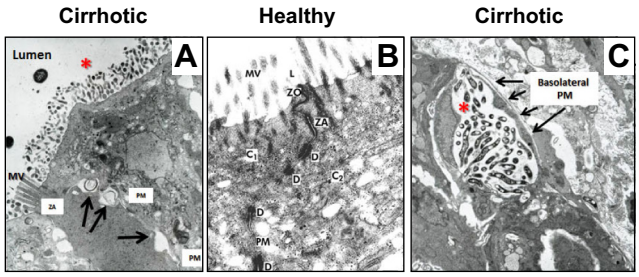

Fig. 1. Electron microscopic image of rat ileum from healthy (B) and cirrhotic rats (A and C). (A) Arrows indicate widening and edema of the intercellular space. Moreover, strong loss of microvilli and adherence of bacteria to the epithelial surface can be appreciated but no bacteria neither intracellular nor in the intercellular space; (C) in contrast, here multiple bacteria are located within the epithelial cell just above the basolateral membrane evidencing transcellular route of crossing the epithelium. MV, microvilli; PM, plasma membrane; ZO, zonula occludens; ZA, zonula adherence; D, desmosome; C, cell; *bacteria. (This figure appears in colour on the web.)

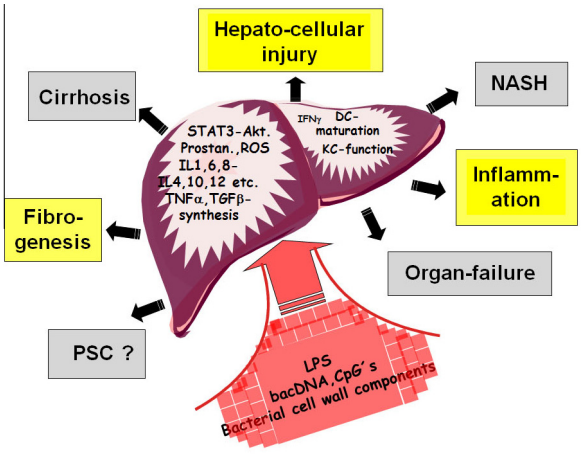

Fig. 2. Hypothetical scheme on impact of bacteria/wall components in the liver (modified after [9]). (This figure appears in colour on the web.)

goblet cells, concentration of antimicrobial peptides) gradually increase along the GI-tract similar to the increasing numbers of microbial organisms present encompassing sufficient firewalls combating the local microbiota. In contrast, number of dendritic cell (DC)-extensions into the intestinal lumen is highest in the proximal small intestine and lowest in the terminal ileum [8] emphasizing the highest degree of host-microbial interaction at the site with the least bacterial load enabling fine-tuning of immune responses at different levels. Therefore, we strongly believe that more research should focus on defence mechanisms and immunological responses to BT within the small intestine in liver cirrhosis.

We completely agree with the second point raised by Dr Matuchansky that the microbiome has a major role in hepatology, and it goes beyond the impact on bacterial infections and/or other complications in liver cirrhosis. In fact, its pathophysiological impact on liver injury, fibrogenesis and inflammation is just starting to be unravelled. However, this was clearly beyond the scope of our review that intended solely to focus on pathological BT in fully established liver cirrhosis and not pre-cirrhotic, fibrotic stages of liver disease and/or conditions of non-alcoholic fatty liver disease (NAFLD)/-steatohepatitis (NASH). In addition, to what has elegantly been summarized we would like to present a modified figure previously published by one of us (Fig. 2). In addition to the role of inflammasomes and effects of pathogen-associated-molecular-patterns (PAMPs) intrahepatically in relation to the colonic microbiota and progression of NASH there are multiple other actions initiated and/or modulated by gut-derived PAMPs on basically any cell type present within the liver. These include but are not limited to synthesis and release of pro-, anti-inflammatory cytokines, chemokines, growth factors, reactive-oxygen species etc. and alteration of diverse intracellular signaling cascades of which much has to be unravelled in the future.

Conflict of interest

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